

Conformational Flexibility and Self-Association of Fibrinogen in Concentrated Solutions

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Abstract

© 2017 American Chemical Society. We studied the hydrodynamic behavior of fibrinogen, a blood plasma protein involved in blood clotting, in a broad 0.3-60 mg/mL range of concentration and 5-42 °C temperature using pulsed-field gradient ^1H NMR-diffusometry. Arrhenius plots revealed the activation energy for fibrinogen diffusion $E_d = 21.3$ kJ/mol at 1.4 mg/mL and 28.4 kJ/mol at 38 mg/mL. We found a dramatic slowdown in fibrinogen self-diffusion with concentration beginning at 1.7-3.4 mg/mL, which deviated from the standard hard-particle behavior, suggesting a remarkable intermolecular entanglement. This concentration dependence was observed regardless of the absence or presence of the GPRP peptide (inhibitor of fibrin polymerization), and also in samples free of fibrin oligomers. By contrast, diffusivity of fibrinogen variant I-9 with truncated C-terminal portions of the $\text{A}\alpha$ chains was much less concentration-dependent, indicating the importance of intermolecular linkages formed by the αC regions. Theoretical models combined with all-atom molecular dynamics simulations revealed partially bent fibrinogen solution conformations that interpolate between a flexible chain and a rigid rod observed in the crystal. The results obtained illuminate the important role of the αC regions in modulating the fibrinogen molecular shape through formation of weak intermolecular linkages that control the bulk properties of fibrinogen solutions.

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